ORIGINAL RESEARCH

Key Words: posttraumatic stress disorder, guanfacine, noradrenergic, norepinephrine, pharmacologic treatment

A Placebo-Controlled Trial of Guanfacine for the Treatment of Posttraumatic Stress Disorder in Veterans

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ABSTRACT ~ Objective: *Preclinical and clinical studies demonstrate a hyperactivity of the norepinephrine system in patients with posttraumatic stress disorder (PTSD). α(2) adrenergic agonists have been shown to ameliorate symptoms of PTSD, likely because of their ability to dampen noradrenergic tone. This study tests the ability of the α(2) adrenergic agonist, guanfacine, to reduce the symptoms of PTSD.* ***Experimental Design:*** *Patients with chronic PTSD were randomized (1:1) to an 8-week double-blind, placebo-controlled treatment of guanfacine followed by a 2–month, open-label extension phase. Patients were maintained on their stable doses of allowed antidepressants during the trial. Efficacy was measured by the following assessment scales: Clinician Administered PTSD Scale (CAPS), Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), and Davidson Trauma Scale (DTS, self-report).* ***Principal Observations:*** *There were no significant differences in the drug versus placebo responses for the clinician-administered or patient self-report outcome measures in this small sample of predominantly male combat veterans with PTSD. However, the medication was well tolerated.* ***Conclusion:*** *Similar to previous findings, this small pilot study failed to show differences in the response to guanfacine versus placebo in a small sample of predominantly male combat veterans with PTSD.* Psychopharmacology Bulletin. *2008;41(1):8-18.*

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INTRODUCTION

There is extensive preclinical and clinical evidence that supports noradrenergic (NE) dysregulation in the pathophysiology of posttraumatic stress disorder (PTSD).[1–5] Rigorous psychophysiologic studies have clearly demonstrated heightened sympathetic nervous system arousal in patients with PTSD,[6] including higher 24-h urinary NE excretion in combat veterans with PTSD compared to controls,[1] a significant downregulation of platelet α(2) adrenergic receptors in combat veterans with PTSD compared to normal controls,[7] and increased flashbacks and panic attacks following a pharmacologic challenge with yohimbine, an α(2) adrenergic antagonist that increases NE release.[8]

Medications that dampen the centrally hyperactive NE state can be beneficial in the treatment of PTSD, including those that decrease NE release (i.e., centrally acting α(2) agonists such as clonidine and guanfacine)[9,10] and those which block postsynaptic NE receptors (e.g., centrally acting α(1) or β receptor antagonists such as prazosin or propranolol).[11–13]

Based on the previous research described earlier, clinical investigators have hypothesized that guanfacine may be as efficacious in reducing PTSD symptoms. Clinically, guanfacine has demonstrated efficacy in other conditions involving catecholamine dysregulation, including some forms of hypertension[14] and attention-deficit hyperactivity disorder.[15–17] To date, there have been case studies describing amelioration of PTSD-related nightmares and other sleep disturbances with guanfacine treatment.[18,19] More recently, an 8-week, double-blind, placebo-controlled trial of guanfacine for the treatment of PTSD was conducted by Neylan et al.[20] in a sample of veterans with chronic PTSD, who were either medication-free or on stable pharmacotherapy. The results of this study failed to show significant differences between guanfacine and placebo in improving the symptoms of PTSD, sleep quality, or general mood.

This paper is a report of a placebo-controlled study of guanfacine as either monotherapy or as an adjunctive medication to SSRI treatment for PTSD in veterans. The study was conducted simultaneously to the Neylan et al.[20] study and serves as an additional and independent examination of the potential efficacy of guanfacine in treating PTSD.

MATERIALS AND METHODS

Patient Selection

The study was conducted in accordance with the Declaration of Helsinki and its amendments. All study participants read and signed an IRB-approved informed consent prior to screening and study participation. The subjects were recruited from the outpatient mental health and

PTSD clinics at the West Haven VA Medical Center (WH-VAMC), Tuscaloosa VA Medical Center (TVAMC), and Birmingham VA Medical Center (BVAMC). The subjects were male and female outpatients, 19–65 years, who met DSM-IV criteria for PTSD based on the Structured Clinical Interview for DSM-IV (SCID-IV).

Inclusion/Exclusion Criteria

Participants eligible for randomization had a primary diagnosis of PTSD as confirmed by the SCID-IV and the Clinician Administered PTSD Scale (CAPS); total CAPS scores were required to be greater than or equal to 45. Participants were not allowed to have substance abuse or dependence for at least 4 weeks prior to randomization, with the exception of nicotine and caffeine. Participants could be either free of psychotropic medication or on stable antidepressant treatment (excluding monoamine oxidase inhibitors) for at least 3 months prior to randomization. Stable treatment with benzodiazepines and/or low dose sedatives such as trazodone for sleep was also allowed.

Antipsychotic medications were not allowed during this trial. In addition, participants were required to have no clinically significant abnormalities on baseline physical or laboratory examination, and female participants of childbearing potential were required to use medically approved methods of birth control. Subjects were excluded for recent use of a monoamine oxidase inhibitor (within the past 6 weeks), presence of substance abuse/dependence during the preceding 4 weeks (except for nicotine/caffeine), lifetime history of schizophrenic, schizoaffective, cognitive, organic mental, or bipolar I disorders, history of sensitivity to guanfacine, active suicidal ideations [based on clinical report or a score $\geq$ 6 on suicide question no. 10 of Montgomery Asberg Depression Rating Scale (MADRS)], active homicidal ideation, legal charges pending with potential of incarceration, clinically significant hepatic or renal disease, low blood pressure ($\leq$90/60), and serious medical or neurological illness (previous myocardial infarction or cerebral vascular accident, arrhythmia, chronic obstructive pulmonary disease, insulin-dependent diabetes mellitus, Parkinson's disease, or epilepsy). Women who were pregnant, planning to become pregnant, or breastfeeding were excluded from the study.

Study Procedures

After review of medical and psychiatric assessments, eligible participants were randomized to either guanfacine vs. placebo for 8 weeks. The subjects were started on 1 mg/day of guanfacine versus placebo. Based on symptomatology and occurrence of side effects, the investigator increased the medication, as tolerated, to 2 mg/day. Current

psychotropic medications were maintained at the previous stable dose. Clinical rating scales were administered and side effects were assessed at baseline and weeks 1, 2, 4, 6, and 8 in the double-blind phase. After completion of the double-blind phase, participants were given the option to continue in an 8-week open-label extension phase during which clinical rating scales were completed at weeks 12 and 16. The following clinical rating scales were completed during each assessment visit: CAPS, Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impression Scale-Improvement (CGI-I), Clinical Global Impression Scale-Severity (CGI-S), Global Assessment of Function, Davidson Trauma Scale (DTS)-self report, Quality of Life Events Scale (self-report), Patient Outcome for Mood Scale (self-report), Quality of Life Enjoyment and Satisfaction Scale Short Form, and Sheehan Disability Scale (SDS).

Statistical Methods

Outcome measures were obtained prior to initiation of treatment (week 0), at weeks 1, 2, 4, and 6, and at the end of treatment (week 8). The criteria for an evaluable case were defined a priori as those patients who took study medication and returned for at least one postbaseline assessment. For the evaluable patients who did not complete treatment, the outcome score from the last assessment completed was carried forward to week 8. For each outcome variable, analysis of covariance (ANCOVA) was used to examine group differences at the end of treatment (week 8), after controlling for the outcome variable at week 0. Treatment effect size (Cohen's *d*) was computed as the difference between drug and placebo groups (drug minus placebo) in adjusted means (week 0 as covariate) divided by the standard deviation of the total sample at week 0. Thus, a negative effect size indicates that the statistically adjusted mean for week 8 is lower for the drug group than for the placebo group.

RESULTS

Patient Sample

Thirty-six patients were randomized (1:1) to guanfacine or placebo treatment (34 men and 2 women). One patient did not return for postrandomization assessment and was not included as an evaluable subject in the analysis. Of the 35 patients who returned for postrandomization assessment, 18 were assigned to guanfacine and 17 to placebo treatment. Twenty-nine patients (83%; 14 drug treatment and 15 placebo treatment) completed the 8 weeks of treatment. Table 1 shows the demographics of each group.

TABLE 1

BASELINE DEMOGRAPHIC CHARACTERISTICS

DEMOGRAPHIC	GUANFACINE (*N* = 18)	PLACEBO (*N* = 17)
Age (years)	53.50 [4.81][a]	53.41 [9.68]
Race (*N*)		
Caucasian	14 (93)[b]	11 (92)
African American	1 (7)	1 (8)
Other	0 (0)	0 (0)
Male gender (*N*)	16 (88.9)	17 (100)
Length of illness (years)	Not coded	Not coded
Comorbid axis I (*N*)		
Major depressive disorder	10 of 14 (71)	10 of 17 (59)
Panic disorder	3 of 14 (21)	1 of 17 (6)
Antidepressant (N)		
SSRI		
Other (list)		

[a]Values in square brackets indicate standard deviations.
[b]Values in parentheses indicate percentages.

Concomitant Medication

All participants in this trial were on stable doses of pharmacotherapy, with the exception of two participants who were treated with guanfacine vs. placebo as monotherapy. The majority of the participants were being treated with a standard antidepressant therapy, including citalopram ($n = 11$), sertraline ($n = 10$), mirtazpine ($n = 2$), nefazodone ($n = 2$), venlafaxine ($n = 1$), combination of bupropion and paroxetine ($n = 1$), and combination of sertraline and mirtazapine ($n = 1$). Patients received adjunctive medications for insomnia, including trazodone ($n = 9$), clonazepam ($n = 10$), alprazolam ($n = 6$), and diazepam ($n = 4$). In addition to antidepressant therapy, one participant was also being treated with methylphenidate and one participant was receiving buspirone. Table 2 shows a detailed listing of concomitant medications.

Placebo-Controlled Phase Outcomes

The results for the primary and secondary outcome measures are summarized in Table 3, which displays means and standard deviations for drug and placebo treatments at the initiation of treatment (week 0) and at the end of treatment (week 8). The significance levels that are reported in Table 3 are from ANCOVAs comparing week 8 scores between groups with week 0 scores included as covariates. Results were

TABLE 2

CONCOMITANT MEDICATIONS

ANTIDEPRESSANT	*N*
SSRIs	
Citalopram	11
Fluoxetine	4
Paroxetine	4
Sertraline	10
Other Antidepressants	
Mirtazapine	2
Nefazodone	2
Venlafaxine	1
Bupropion	4
Trazodone	9
Benzodiazepines	
Alprazolam	6
Clonazepam	10
Diazepam	4
Other	
Methylphenidate	1
Buspirone	1

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similar when changes during treatment (linear regression slopes or change scores) were compared between drug and placebo groups.

None of the differences between drug and placebo groups was significant. For CAPS total score, which was the primary outcome measure, there was essentially no difference between drug and placebo groups at the end of treatment after adjusting for pretreatment scores. None of the differences for the CAPS subscales or for scores from the DTS, MADRS, SDS, or QOL approached significance. The difference for CGI-S was borderline significant; there was a trend for more improvement in CGI-S ratings across the 8 weeks of treatment in the drug group than in the placebo group.

Drug and placebo groups showed no tendency to differ across treatment, and effect sizes were similar for PTSD symptom ratings obtained by interview (i.e., the CAPS) and by self-report (i.e., the DTS). There was a tendency, which was sometimes significant, for higher week 0 scores to predict less symptom improvement during treatment. This relationship is illustrated in Table 4 for treatment changes (week 8 minus week 0) in CAPS total scores, DTS total scores, and MADRS scores as a function of initial CGI-S ratings. As indicated in Table 4, increasing improvement in DTS total scores during treatment was significantly associated with lower CGI-S ratings in the initial assessment,

TABLE 3

COMPARISONS OF GUANFACINE TREATMENT ($N = 18$) WITH PLACEBO ($N = 17$) IN INTENT-TO-TREAT ANALYSES

	MEAN					
	GUANFACINE		PLACEBO		EFFECT	
	WEEK 0	WEEK 8	WEEK 0	WEEK 8	SIZE	*p*
CAPS						
Total score	82.06 (16.81)[a]	66.94 (29.87)	88.41 (17.87)	74.82 (29.26)	−0.09	.967
Reexperiencing	21.50 (6.94)	16.83 (10.41)	23.06 (7.50)	17.94 (10.50)	0.06	.896
Avoidance	34.72 (9.74)	29.61 (11.55)	38.18 (6.30)	34.06 (11.11)	−0.12	.502
Hyperarousal	25.83 (6.30)	20.50 (10.62)	27.18 (7.32)	22.82 (9.06)	−0.15	.689
DTS						
Total score	92.33 (22.50)	75.11 (32.51)	100.77 (24.74)	82.59 (31.04)	0.04	.889
Reexperiencing	24.61 (7.31)	18.78 (10.47)	24.77 (12.58)	21.06 (10.05)	−0.21	.467
Avoidance	38.17 (10.47)	33.61 (13.36)	43.47 (7.84)	36.12 (13.95)	0.29	.434
Hyperarousal	29.56 (7.75)	22.72 (12.39)	32.53 (6.87)	25.41 (9.77)	0.04	.712
MADRS	28.78 (5.92)	24.00 (8.70)	30.94 (6.32)	27.06 (10.26)	−0.15	.717
CGI-S	4.89 (0.83)	4.33 (1.03)	4.82 (0.64)	4.76 (0.97)	−0.68	.071
SDS	19.06 (6.40)	18.61 (8.46)	23.65 (5.64)	19.82 (8.41)	0.53	.238
QOL	42.78 (7.71)	43.89 (9.25)	40.77 (8.95)	41.59 (8.73)	0.03	.755

[a]Values in parentheses indicate SDs.

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and the same trend was present for CAPS total scores and MADRS scores. When treatment (drug versus placebo) was added to these analyses, the interactions of initial CGI-S with treatment were not significant ($p > .20$ for all) for any of these three variables.

Open Label Extension Phase Outcome

Twenty-four patients completed the 8 weeks of treatment and an additional 8 weeks in the open-label extension phase. Ten of these follow-up patients were from the placebo group, and 14 had been treated

TABLE 4

CHANGES IN CAPS, DTS, AND MADRS SCORES DURING 8 WEEKS OF TREATMENT AS A FUNCTION OF INITIAL CGI-SEVERITY RATING

	CGI-SEVERITY RATING						
	MODERATELY ILL ($N = 12$)		MARKEDLY ILL ($N = 16$)		SEVERELY ILL ($N = 7$)		
SCALE	MEAN	SD	MEAN	SD	MEAN	SD	p
CAPS total score	−23.67	22.06	−12.00	17.39	−3.86	11.57	.073
DTS total score	−31.67	20.30	−12.25	18.80	−6.14	13.36	.009
MADRS	−7.00	6.49	−3.00	7.68	−2.86	7.24	.302

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with the drug from the outset. CAPS total scores were compared for the two treatment conditions for weeks 0, 8, and 16. A 2 × 3 repeated measures ANOVA did not reveal any overall group difference, $F(1, 22) = 0.00$, $p > .50$, and the interaction of treatment duration (weeks 0, 8, and 16) and group (drug versus placebo) did not approach significance, $F(2, 44) = 0.69$, $p > .50$. Although the treatment duration effect was highly significant, $F(2, 44) = 24.24$, $p < .001$, across the 16 weeks, the decrease in CAPS total scores occurred during the first 8 weeks. The change from week 8 to week 16 was not significant, $F(1, 22) = 1.32$, $p > .25$, and there was no group by open label treatment (week 8 versus week 16) interaction, $F(1, 22) = 1.05$, $p > .25$. Thus, among the 24 patients who completed treatment and were available for follow-up, there was a substantial decline in rated PTSD symptoms during the 8 weeks of treatment. The decrease did not continue in the 8 weeks of open label extension, but there was also no tendency for the rated PTSD symptoms to increase during those 8 weeks. Moreover, the two groups did not differ in their response to treatment (change from week 8 to week 16) during the open-label extension.

Safety and Tolerability

Adverse drug events indicated as possibly related to study drug included dizziness experienced by two patients in the guanfacine group, sleeplessness experienced by two patients in the guanfacine group, one instance of diarrhea in the placebo group, and one instance of increased sexual dysfunction in the placebo group. Two patients in the guanfacine group experienced dry mouth, with one patient experiencing a severe episode resulting in epistaxis. Dry mouth is a known side effect of guanfacine. Table 5 provides a summary of adverse events.

There were no serious adverse events determined to be directly related to guanfacine.

TABLE 5

ADVERSE EVENTS

ADVERSE EVENTS	GUANFACINE	PLACEBO
Possibly related	Dry mouth (3)	Increase in sexual dysfunction
	Fatigue (3)	Indigestion
	Dizziness (2)	Diarrhea
	Increased sedation (2)	Cough and fever
Probably not related	Panic attack	Constipation
	Nausea	
	Diarrhea	
Not related	Headache secondary to nightmare	
	Arm and neck pain	
	Tinea pedis	

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DISCUSSION

This 8-week placebo-controlled trial of adjunctive guanfacine for PTSD in veterans replicates the negative findings of Neylan et al.[20] Guanfacine relative to placebo did not result in a greater level of symptom improvement in PTSD and depression or reported quality of life. The study population was predominantly male. All of the participants presented with chronic combat related PTSD and ~94% were on stable doses of pharmacotherapy. Therefore, the study participants may reasonably be considered a treatment refractory group that may help to explain the negative findings. Even though guanfacine was associated with more side effects than placebo, the study drug was relatively well tolerated. The CAPS and DTS total scores did not suggest any tendency for differential improvement in PTSD symptoms, and none of the group differences in CAPS and DTS subscales approached statistical significance. Overall, these findings show no indication of symptom improvement resulting from the administration of guanfacine.

Because sample size was small, the power to detect treatment effects was limited. However, baseline scores were well correlated with those obtained at the end of treatment, and the power values for the ANCOVAs were not unreasonably low. For example, the correlation of baseline and posttreatment CAPS total scores was $r = .78$. Therefore, the power to detect a medium effect between drug and placebo groups was .62 for CAPS total scores, and the power to detect a large effect was .95. Correlations between baseline and posttreatment scores for the other scales in Table 3 ranged from .53 to .79, and the power to detect large effects ranged from .77 to .96.

These considerations imply that the test of group differences for the primary outcome measure (i.e., CAPS total score) was reasonably sensitive. There was a high likelihood of detecting a large effect, and the probability of detecting a medium effect was better than .6. The likelihood that a large difference in CAPS total scores went undetected is .05, and the largest probability of an undetected large effect for the CAPS subscales is only .13.

The results of our study, as in the case of the Neylan et al.,[20] are not contradictory to the results of the Raskind et al.,[21] which found that prazosin, a specific adrenergic postsynaptic α(1) antagonist, reduces trauma nightmares and improves sleep quality in veterans with chronic PTSD. Guanfacine lowers synaptic availability of norepinephrine for all adrenergic receptors, possibly negating any potential positive benefits of the drug acting to reduce α(1) activation.

CONCLUSION

In this second placebo-controlled study, guanfacine as an adjunctive treatment to antidepressants has failed to demonstrate efficacy in a treatment-resistant, predominantly, male combat veteran population. The lack of efficacy of guanfacine in a veteran population cannot be generalized to the civilian or predominantly female population, since other agents have shown discrepancies in outcomes between veteran and civilian groups. ✤

ACKNOWLEDGMENTS

This study was funded by a VA Merit Award (Principal Investigator Steven Southwick, MD) The authors acknowledge financial support of VA Research and Development and the following research coordinators and clinical raters involved with the collection of this data: Elizabeth Frazier, MS; Elizabeth B. Waldrop, RN; Sheila Essary, LPN; Stephanie K. Wallace, MS; Sandra Ambrose, MSN; and Raela Williford, Pharm.D.

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